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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/776,865	02/02/2001	Carl G. Hellerqvist	22100-0100 (46126-252687)	7056

7590 07/16/2003

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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	10

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/776,865	HELLERQVIST, CARL G.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-38 and 40-58* is/are pending in the application.

4a) Of the above claim(s) *2,17-28,49-54,57 and 58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-16,29-38,40-48,55 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,2,4-38 and 40-58* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. The amendment filed April 21, 2003 in Paper No. 9 is acknowledged and has been entered. Claims 3 and 39 have been canceled. Claims 1, 4-6, 8-12, 14-16, 29, 30, 32, 35, 37, 38, 40-42, 44-46, 48, and 55 have been amended.

2. Claims 1, 2, 4-38, and 40-58 are pending in the application. Claims 2, 17-28, 49-54, 57, and 58 have been withdrawn from further consideration pursuant to 37 CFR § 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

3. Claims 1, 4-16, 29-38, 40-48, 55, and 56, insofar as the claims are drawn to elected invention, are currently under prosecution.

Grounds of Objection and Rejection Withdrawn

4. Unless specifically reiterated below, the grounds of objection and rejection set forth in the previous Office action mailed October 21, 2002 (Paper No. 7) have been withdrawn.

For clarity of record, the rejection of claims 1, 5, 29-34, 37, 40, 41, 43, and 44 under 35 USC § 102(b), as anticipated by Nair et al., for the reason set forth in section 13 of the previous Office action has been withdrawn because the amendment filed April 21, 2003 limits the claims to a method comprising administering to a mammal a composition comprising HP59 or SP55. As HP59 and SP55 are polypeptides expressed in human and sheep, the composition of the prior art would not be expected to contain either polypeptide, because the composition of the prior art was derived from mouse.

Furthermore, the rejection of claims 2-14 and 40-48 under 35 USC § 112, second paragraph for the reason set forth in the 4th paragraph of section 11 of the previous Office action has been withdrawn because the specification explicitly defines "substantial identity" as having at least 80% identity.

Objection to Amendment

5. The amendment filed April 21, 2003 in Paper No. 9 is objected to because at page 11, which is headed "PENDING CLAIMS", claim 7 differs from claim 7, as originally filed, but claim 7 has not been amended. However, it is noted that in view of Applicant's remarks, it appears that Applicant intended to amend claim 7 to read as the claim appears at page 11.

Specification

6. The specification is objected to because the use of numerous improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Additional examples, which were not given in the previous Office action, include GENBANK (page 5), Genzyme™ (page 12), Applied Biosystems™ (page 15), and American Type Culture Collection™ (page 18).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicant may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Claim Objections

7. Claims 14, 44, and 48 are objected to because the claims have been amended to recite the phrase "a peptide encoded by amino acid residues". The recitation renders the claims objectionable because a peptide is not encoded by amino acid residues, but rather by polynucleotide residues.

Furthermore, claim 44 is objected to because of the typographical error reading "SEQ ID NO:1"; the peptides to which the claims refer are fragments of the amino acid sequence set forth in SEQ ID NO: 2. SEQ ID NO: 1 is a polynucleotide sequence encoding SEQ ID NO: 2. Therefore, claim 44 should recite, for example, "a peptide consisting of amino acid residues 49-63 of SEQ ID NO: 2".

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1 and 4-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being reasonably enabling for a method for preventing melanoma in mice immunized with "HP59/CFA", does not reasonably provide enablement for a method for preventing cancer in a mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the reasons set forth in section 8 of the previous Office action mailed October 21, 2002 (Paper No. 7).

Claims 30-38 and 40-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being reasonably enabling for a composition consisting of a mixture of Hab1, Hab2, and Hab3, or alternatively consisting of a mixture of p55a, p56a, p57a, Hab1, and Hab2 for attenuating tumor burden in mice challenged with melanoma or Lewis lung tumor cells and reasonably enabling for a method for protecting against the development of melanoma in mice immunized with "HP59/CFA", does not reasonably provide enablement for a composition for protecting against or attenuating cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention commensurate in scope with these claims for the reasons set forth in section 8 of the previous Office action mailed October 21, 2002 (Paper No. 7).

Claims 55 and 56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing a composition consisting of a mixture of Hab1, Hab2, and Hab3, or alternatively consisting of a mixture of p55a, p56a, p57a, Hab1, and Hab2 for attenuating tumor burden in mice challenged with melanoma or Lewis lung tumor cells and reasonably enabling for a method for producing a composition consisting of "HP59/CFA" for protecting against the development of melanoma in mice, does not reasonably provide enablement for a method for producing a composition for treatment and/or prevention of cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the reasons set forth in section 8 of the previous Office action mailed October 21, 2002 (Paper No. 7).

Applicant has traversed these grounds of rejection arguing that "one skilled in the art would extrapolate the data provided in the specification showing the effectiveness of the invention for preventing melanoma in mice immunized with HP59/CFA to decreasing the incidence of cancer in mammals generally" (Paper No. 9, page 17, paragraph 3). Applicant has contended that experimental data generated using mice is routinely extrapolated to mammals in general. Applicant has remarked that the references used as the basis of the rejection were published in the years 1994, 1995, and 2000 and has therefore submitted: "Although the early stages of cancer vaccine development were faced with skeptism and challenge, more recent findings have reinstated confidence in the development of effective vaccines that can not only treat various manifestations of cancer, but also prevent them" (page 18, paragraph 4). Applicant has cited Espinoza-Delgado (*The Oncologist* **7**: 20-33, 2002) in support of this assertion.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Espinoza-Delgado teaches, "the field of cancer vaccines is **in** an early stage of development" (emboldened for emphasis; abstract). As Applicant has pointed out,

Espinoza-Delgado teaches, "**in som cases**, [the tumor specific immune responses induced by cancer vaccines are] associated with clinical responses" (emboldened for emphasis; abstract). Unfortunately, however, clinical responses have more often not been achieved, as evidenced by the teachings of the numerous references cited in the previous Office action in support of this ground of rejection. Even more recently, Espinoza-Delgado discloses, for example, at page 5 of 21, as Applicant has provided the reference:

> Vaccine trials using some of the aforementioned antigens recently have begun and are providing substantial information about the type of immune responses that are elicited. These studies are in relatively early stages and only few vaccines have entered later stages of clinical testing. Although current results are not final, some conclusions can be drawn. First, CTL responses can be induced by peptide vaccination; second, the presence of an expanded pool of TAA [tumor associated antigen]-specific T cells does not lead to tumor regression.... [Citations omitted.]

It is duly noted in reply to Applicant's remarks, the same conclusion was drawn by some of the authors of the references that were cited in the previous Office action. For example, Lee et al. discloses that despite the induction of antitumor T cell activity in the subjects, tumor regression was not observed.

Additionally, it is noted that Espinoza-Delgado refers to the results of a study in which "curiously, [...] patients who achieved clinical response had a decreased T-cell response" (page 5 of 21). Thus, clinical responses were only achieved paradoxically in patients who may not have responded to the vaccine; although Espinoza-Delgado suggest that other explanations are possible, clearly further research is needed to determine the reasons that clinical responses were achieved in only patients having seeming poor immune responses to the vaccine.

Furthermore, Espinoza-Delgado discloses at page 7 of 21:

> The majority of the clinical trials using the DC [dendritic cell]-based cancer vaccine approach have been performed in patients with metastatic melanoma. Although early studies using peptide-pulsed DC clearly demonstrated antigen-specific immune responses both to the immunizing peptide and to autologous tumor, no clinical responses were observed. [Citation omitted.]

Again, it is duly noted in reply to Applicant's remarks, the authors of the references that were cited in the previous Office action disclosed similar observations. For example,

Zaks et al. teaches that vaccination with a peptide fragment of a tumor-associated antigen leads to the induction of a peptide-specific T cell response, but the antigen-specific T cells failed to recognize tumors expressing the antigen. Gao et al. teaches that although antitumor CTL response could be induced in a subject, the subject's tumors failed to regress, which Gao et al. suggests probably resulted from a failure of the antitumor CTL to migrate to the anatomical sites of the tumors.

Even where promising results have been achieved, Espinoza-Delgado teaches, for example: "Although the tumor-APC hybrid strategy has enormous potential, there are several questions that need to be addressed if this approach is to become widely used in clinical trials" (page 11 of 21). Therefore, despite promise, Espinoza-Delgado teaches that more research must be performed before such cancer vaccines can be used *in a clinical trial*, never mind in a clinical setting to prevent cancer in any mammal, particularly a human.

Espinoza-Delgado concludes at page 13 of 21:

> As we begin to widen our knowledge significantly, we will be in a position to better comprehend the barriers to successful immunotherapy for cancer. [...] Despite the significant advances that are occurring in the field, cancer vaccine strategies need to be optimized to obtain more favorable clinical outcomes.

In view of the disclosures of Espinoza-Delgago, it appears contrary to Applicant's assertions that the art is still today in its scientific infancy, which as Bodey et al. similarly commented in 2000, is despite several decades of clinical and basic research.

Nevertheless, because Applicant has argued that due to the age of the references cited in the previous Office action, the predictability, skill, and state of the art is not fairly or accurately measured, Applicant is referred to the teachings of Yu et al. (*Journal of Clinical Investigation* **110**: 289-294, August 2002). Yu et al. disclose in the abstract:

> A decade ago, it seemed clear that our burgeoning knowledge of the molecular identities of tumor-associated antigens and a deeper understanding of basic immunology would point the way to an effective therapeutic cancer vaccine. Significant progress has been made and objective regressions after immune-based treatments are observed in some patients – even in those with bulky, metastatic disease. Notwithstanding this progress, we do not have a cancer vaccine in hand that can reliable increase patient survival or induce tumor destruction.

Finally, in reply to Applicant's remarks that the skilled artisan routinely extrapolates experimental data generated using mice to reliably predict the outcome of treatments in mammals, including humans, Bodey et al. and Gura, for example, teach that to the contrary, the skilled artisan cannot extrapolate experimental data generated using mice or other animal models to accurately predict the effectiveness of treatment modalities in humans. Moreover, clinical trials of cancer vaccines have generally met with little success, despite the promise of pre-clinical studies.

In view of the preponderance of evidence of record, the ground of rejection set forth in section 8 of the previous Office action is maintained.

10. Claims 55 and 56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth in section 9 of the previous Office action mailed October 21, 2002 (Paper No. 7).

In view of Applicant's remarks, it appears that Applicant intended to amend claim 55 to obviate this ground of rejection; nevertheless, claim 55 has not been amended and therefore this ground of rejection of claims 55 and 56 is maintained.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons set forth in the 5th paragraph of section 11 of the previous Office action mailed October 21, 2002 (Paper No. 7).

In view of Applicant's remarks, it appears that Applicant intended to amend claim 7 so as to obviate this ground of rejection, but as noted in the objection to the amendment above, claim 7 has not been amended.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 4, 6, 7, 15, 16, 55, and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Nair et al. (*International Journal of Cancer* **70**: 706-715, 1997) for the reason set forth in the section 13 of the previous Office action mailed October 21, 2002 (Paper No. 7).

Applicant has traversed this ground of rejection arguing that the disclosure of the prior art does not anticipate the claimed invention for the following reason: "The present invention is directed to a cancer vaccine that targets a unique protein that is expressed in mammals after a short period following birth, *but only* in mammals having a pathoangiogenic condition" (italicized in the original; Paper No. 9, paragraph bridging pages 20 and 21). Applicant therefore contends that the methods of the prior art differ from that which is claimed, since the prior art teaches "a vaccine that results from the use of proteins or peptides encoded by antigens derived from tumor cells from patients" (page 21, paragraph 1).

Applicant's argument has been carefully considered but not found persuasive. Claim 1 is drawn to a method for preventing cancer in a mammal *comprising* administering to the mammal an amount of at least one Group B β-hemolytic Streptococci (GBS) toxin receptors effective to induce or maintain an immune response to the GBS toxin receptor, wherein said GBS toxin receptor has substantial identity to SEQ ID NO: 2. Absent a showing of any difference, the composition of the prior art, which is administered to the mammal, is deemed to comprise an amount of a GBS toxin receptor having substantial identity to SEQ ID NO: 2, which is effective to induce or maintain an immune response to HP59. The mice to which the composition of the prior

art is administered *have* a pathoangiogenic condition, namely cancer. Therefore, the method of the prior art and the claimed method are deemed the same, again absent a showing of any difference.

Conclusion

15. No claims are allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. This application contains claims 2, 17-28, 49-54, 57, and 58 drawn to an invention nonelected with traverse in Paper No. 5. A complete reply to this final rejection must include cancellation of nonelected claims or other appropriate action, as set forth under 37 CFR § 1.144. See MPEP § 821.01.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
July 11, 2003

YVONNE EYLER, PH.D
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